Comm.
Dr. Andervont
Dr. Gardner
Dr. Huebner

CARCINOGENESIS

#763AR2
#763AR1-7/1/72-6/30/73
#763A-7/1/71-6/30/72
#763-7/1/70-6/30/71

THE COUNCIL FOR TOBACCO RESEARCH—U.S.A., INC.
110 EAST 59TH STREET
NEW YORK, N. Y. 10022
(212) 421-8585

RECEIVED
FEB 5 1973

Application for Research Grant
(Use extra pages as needed)

Date: January 29, 1973

1. Principal investigator (give title and degrees):

John W. Parker, M.D. — Associate Professor of Pathology
Richard L. O'Brien, M.D. — Associate Professor of Pathology

2. Institution & address:

Department of Pathology
University of Southern California School of Medicine
2025 Zonal Avenue
Los Angeles, California 90033

3. Department(s) where research will be done or collaboration provided:

Department of Pathology

4. Short title of study:

"Immune Suppression by Cigarette Smoke and Chemical Carcinogens"

5. Proposed starting date: July 1, 1973

6. Estimated time to complete: Two years

7. Brief description of specific research aims:

We wish to determine whether cigarette smoke inhalation or the parenteral administration of chemical carcinogens, some of which are components of cigarette smoke, suppress cellular immunity when measured by in vitro assays of lymphocyte activation. In brief, we shall determine the effects of cigarette smoking and of chemical carcinogens on the ability of mouse lymphocytes to undergo blastic transformation in response to the non-specific mitogens phytohemagglutinin (PHA), pokeweed mitogen (PWM) and Na IO_4, and in a mixed leukocyte culture (MLC) assay.

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8. Brief statement of working hypothesis:

It has been postulated for sometime and by a number of investigators that one of the mechanisms involved in oncogenesis is the suppression of the immune response of the host so that its surveillance against spontaneously arising or induced neoplastic cells is faulty. In the face of this faulty surveillance system the neoplastic cells may establish themselves to the extent that the immune mechanism is no longer capable of eliminating them. It has been shown in the past that chemical carcinogens can suppress humoral and cellular immunity. The hypothesis that we are testing is that cigarette smoke or purified chemical carcinogens may suppress cellular immunity and that this suppression can be measured by in vitro functions of lymphocytes. The importance of testing this hypothesis is based on the premises that lymphocytes are important mediators of cellular immunity and that the in vitro assays of lymphocyte transformation reflect lymphocyte function in vivo.

9. Details of experimental design and procedures (append extra pages as necessary)

Background:

There is a good deal of information in the literature which suggests that the destruction of neoplastic cells in vivo and in vitro involves the direct attack of sensitized lymphocytes on target neoplastic cells. In this respect it resembles transplantation rejection phenomena and involves the cellular immune system in neoplastic cell destruction. It has been postulated that deficiencies in the cellular immune system may allow either induced or spontaneously arising neoplastic cells to survive and establish themselves as tumors. These considerations have led us to undertake studies attempting to determine the effects of carcinogens on the functional integrity of the cellular immune system.

There are several ways to assay the integrity of cellular immunity. That which we use is the measurement of in vitro responses of lymphocytes to blastogenic and mitogenic stimuli. It has been demonstrated in the past that chemical carcinogens, particularly polycyclic hydrocarbons, are capable of suppressing the cellular and humoral immune responses. These studies have utilized for the most part in vivo assays. These are useful for measuring in vivo functional integrity but are limited in their ability to provide an opportunity to study cellular and subcellular mechanisms by which immune suppression occurs. For this purpose the in vitro assays of lymphocyte transformation in response to blastogenic stimuli are advantageous. Our laboratories utilize the response of lymphocytes to PHA, PWM, Na IO_4 and MLC by blastic transformation. These in vitro assays of lymphocyte functional integrity are useful because they are simple, highly reproducible and not time consuming. Further, the MLC assay represents the ability of the lymphocytes to recognize as abnormal or foreign the surface of other cells. It is expected that it is this recognition which enables lymphocytes to destroy neoplastic cells when they arise in vivo. The validity of these in vitro assays as a measure of in vivo function of the lymphocytes is supported by the findings of a number of investigators that the depression of lymphocyte responsiveness to PHA and other mitogens in vitro is correlated with clinically evident immunologic depression when it occurs either as a component of a disease state or when induced with immunosuppressive agents.

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For the last two and a half years the Council for Tobacco Research has supported our studies of the effects of carcinogenic chemicals on these in vitro lymphocyte functions. We have measured the effects of chemicals administered to lymphocytes in vitro and given in vivo to experimental animals. To the present time, we have found that the chemical carcinogens dimethylbenz-anthracene (DMBA) and 4-nitroquinoline-N-oxide (4-NQO), when administered to the cells in vitro, inhibit their responses to PHA, PWM and MLC. This inhibition occurs at low concentrations in the neighborhood of 10^{-7} to 10^{-6}M. We have also found that non-carcinogenic but related compounds, specifically pyrene and benzanthracene, do not inhibit these reactions when administered in vitro. The effects of in vitro administration of hydrocarbons is not perfectly correlated with the carcinogenicity of the compounds used. For example, we have also found that methylcholanthrene (MCA), a potent carcinogen, does not inhibit the response of cells to PHA or PWM. It does inhibit transformation in MLC but the inhibition requires higher concentrations of MCA than of DMBA and 4-NQO.

We have also conducted studies attempting to measure the effect of these carcinogens when administered in vivo. We have injected MCA subcutaneously into C57 black mice. At varying times after exposure to the hydrocarbon, we have sacrificed the mice and measured the ability of their cells to respond to PHA and MLC stimulation. At the present time the results are preliminary but they indicate that the administration of the carcinogenic compound suppresses the ability of lymphocytes to respond to the in vitro mitogenic stimuli. This is not so in the control group. Interestingly, these decreases precede and coincide with the appearance of tumors in the animals treated with carcinogen. The preliminary nature of the experiments done so far is due to the fact that the mitogenic assays on our mice have been complicated by apparent exogenous antigenic stimulation of the lymphocytes so that in all our assays we have a rather high background of lymphocyte transformation. Consequently the amount of suppression of in vitro induced transformation by carcinogens is difficult to quantitate. We have dealt with this technical problem by doing our experiments on specific pathogen-free mice kept in isolation to diminish exogenous antigen stimulation. These measures and exploring various proportions of stimulator and responder cells in MLC have resolved the technical problem and our assays now have very low background transformation. Thus over the next four to five months we will be gathering data which will allow us to quantitate quite confidently the effect of carcinogens on the ability of the lymphocytes to respond to the in vitro mitogenic stimuli provided by PHA, PWM and MLC.

We wish to extend these studies to a larger group of carcinogenic chemicals, including other classes of carcinogenic compounds. We wish also to extend them to determine the effects of chronic cigarette smoking on these in vitro measures of lymphocyte functional integrity. We have already done one assay of in vitro transformation of lymphocytes from smoke exposed mice in Dr. Clayton G. Loosli's laboratory. The results were inconclusive because our control mice were a different strain of C57 black mice, a great deal younger and had been breathing ambient Los Angeles air, but they were sufficiently interesting to stimulate our desire to conduct a carefully controlled study.

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During the period of support by the Council for Tobacco Research we have also developed and explored another assay for in vitro measurement of lymphocyte function. This is a system for the transformation of lymphocytes by a short treatment with Na IO_4. We have published several papers on this transformation (see accompanying progress note) and we wish now to include it as an in vitro measure of lymphocyte functional integrity in the mice which we are challenging with chemical carcinogens and with chronic cigarette smoking. In general terms it is similar to the in vitro transformation stimulated by PWM and PHA, but it is sufficiently different, particularly with reference to the cell population stimulated, that we feel it is an important addition to our studies.

Experimental Design:

To measure the effect of cigarette smoking on lymphocyte responses to the in vitro mitogenic stimuli we will use to a large extent the same mice that Dr. Clayton G. Loosli is using in his studies of the effects of cigarette smoke on the lungs of mice.

C57 black, CD1 and Snell mice (pathogen-free) will be exposed to smoke from three standard low nicotine cigarettes in a single exposure per day in a CTR-Walton horizontal smoke exposure machine. Control mice will spend an equal time in the smoke exposure machine but they will be breathing filtered air. Control and smoke exposed mice will be housed in separate but identically constructed filtered air rooms. Groups of mice exposed to smoke of three cigarettes per day will be sacrificed at three month intervals and the responses of their lymphocytes to PHA, PWM, Na IO_4 and MLC will be measured. Groups of mice will also be removed from smoke exposure at varying times and their lymphocytes will be studied at intervals thereafter to determine whether any changes observed during the smoking period are progressive, static or reversible. All experiments on lymphocyte transformation will be correlated with Dr. Loosli's studies on the pulmonary lesions occurring in these mice. In all experiments, an appropriate number of non-smoking control mice of the same age as the experimental animals will be sacrificed and their lymphocytes studied in the same manner.

The design for studying the effects of purified carcinogens on in vitro lymphocyte transformation will be similar to that which we are following now. We will select compounds from the benzacridine, the nitrosamine and the polycyclic hydrocarbon classes of chemical carcinogens and structurally related non-carcinogenic analogs for test. The chemical carcinogens and control compounds will be dissolved in trioctanoin or other suitable solvents and injected subcutaneously into mice, either in single doses or as a cumulative dose spaced over a period of several weeks. At varying times thereafter they will be sacrificed and the responses of their lymphocytes to PWM, PHA, Na IO_4 and MLC will be assayed.

The experimental animals will be specific pathogen-free C57 black mice which will be kept in an isolated environment to prevent their contacting exogenous infectious agents and other antigenic stimuli. Stimulator cells for use in the MLC will be derived from spleens of CBA mice and treated with mitomycin-C to prevent their blastic transformation in the culture system. All of these methods are currently in use in our laboratories.

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10. Space and facilities available (when elsewhere than item 2 indicates, state location):

Facilities currently available for this research are the combined research spaces of Drs. O'Brien and Parker. This includes 3,000 sq.ft. of research space in the Hoffman Research Building plus 1,000 sq.ft. of communally shared research space in the same building. This program has available to it the facilities and technical expertise necessary for a wide variety of experimental procedures. These include tissue culture, biochemical and biophysical procedures and electron microscopy.

A list of the major equipment available for this research in our laboratories includes three electron microscopes, a Coulter counter and cell size plotter, a Zeiss photomicroscope, several light, phase and dissecting microscopes, Beckman models L4 and L3-50 ultracentrifuges, a Sorvall refrigerated high speed centrifuge, two refrigerated International low speed centrifuges, two liquid scintillation counters, spectrophotometers, a spectrophotofluorometer, incubators for cell cultures, and darkroom facilities. We also have available to us the facilities of the University of Southern California School of Medicine Vivarium for the procurement and custody and care of experimental animals.

11. Additional facilities required:

None.

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12. Biographical sketches of investigator(s) and other professional personnel (append): Appended.

13. Publications: (five most recent and pertinent of investigator(s); append list, and provide reprints if available). Appended.

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14. First year budget:

A. Salaries (give names or state "to be recruited")		% time	Amount
Professional (give % time of investigator(s) even if no salary requested)			
John W. Parker, M.D.	Investigator	40% *	-
Richard L. O'Brien, M.D.	Investigator	10%	-

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Technical		
Joan Steiner, M.D.	Research Assistant	100%
Jo Ann Vukmanovich	Laboratory Assistant	100%
	Fringe Benefits, 10%	

REDACTED

Sub-Total for A

B. Consumable supplies (by major categories)

Tissue culture supplies	3,000
Chemicals	2,000
Animals, purchase and care	6,000
	11,000

Sub-Total for B

C. Other expenses (itemize)

Travel - One national meeting for each investigator	900
Publication costs	200
Sub-Total for C	1,100
Running Total of A + B + C	33,000

D. Permanent equipment (itemize)

None

Sub-Total for D

E. Indirect costs (15% of A+B+C) E 4,950

Total request 37,950

15. Estimated future requirements:

	Salaries	Consumable Suppl.	Other Expenses	Permanent Equip.	Indirect Costs	Total
Year 2	R	12,000	1,100	none	5,257	40,302

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16. Other sources of financial support:
List financial support from all sources, including own institution, for this and related research projects.

CURRENTLY ACTIVE

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
Mechanisms of Suppression of Cellular Immunity by Carcinogenic Hydrocarbons	Council for Tobacco Research-USA, Inc. #763AR1	29,890	7-1-72 to 6-30-73
Mechanisms of Environmental Carcinogenesis	John A. Hartford Foundation, Inc.	161,266	5-1-72 to 4-30-74
Special Fellowship for a sabbatical year at the Walter & Eliza Hall Institute of Medical Research, Melbourne, Australia (J.W. Parker)	National Cancer Institute, NIH #1-FO3-CA-52894-01	14,000 (stipend) + travel	9-1-72 to 8-31-73

PENDING OR PLANNED

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
Lymphocyte Transformation by Periodate	Department of Health, Education & Welfare, NIH	88,865	7-1-73 to 6-30-76 (3 yrs)

It is understood that the investigator and institutional officers in applying for a grant have read and accept the Council's "Statement of Policy Containing Conditions and Terms Under Which Project Grants Are Made."

Principal Investigator John W. Parker, M.D.
Typed Name Richard L. O'Brien, M.D.
Signature Richard L O'Brien John W Parker Date 1-29-73
Telephone 213 (Area Code) 225-1511 (Number) 392 or 387 (Extension)

Check's payable to
University of Southern California
c/o Mr. Clark A. McCartney, Director,
Mailing address for checks Dept. Contracts & Grants
University of Southern California
University Park, Los Angeles, Calif. 90007

Responsible officer of institution
Typed Name Mr. Z. A. Kaprielian, Vice President,
Title Academic Administration and Research
Signature [signature] Date JAN 31 1973
Telephone 213 225-1511 432

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R: REDACTED MATERIAL

BIOGRAPHICAL SKETCH — JOHN W. PARKER, M.D.

Name: John W. Parker, M.D.
Academic Title: Associate Professor of Pathology
Date of Birth: REDACTED
Citizenship:
Sex: Male
Marital Status: REDACTED

EDUCATION:

Institution and location	Degree	Year	Scientific Field
University of Arizona, Tucson, Arizona	REDACTED		Zoology
Harvard Medical School, Boston, Mass			Medicine

HONORS:

Phi Beta Kappa, Phi Kappa Phi, Phelps Dodge Scholarship	University of Arizona	1949-1953
Marshall Foundation Scholarship,	Harvard Medical School	1953-1959
Dernham Sr. Fellow in Oncology,	Am. Cancer Soc. (Calif)	1964-1969

RESEARCH AND PROFESSIONAL EXPERIENCE:

1972-1973	Visiting Sr. Research Fellow, Walter & Eliza Hall Institute of Medical Research, Melbourne, Australia (Sponsor: Dr. Donald Metcalf, Head, Cancer Research)
1968-present	Associate Professor of Pathology, University of Southern California School of Medicine, Los Angeles.
1969-present	Head, Electron Microscopy Section, Department of Pathology, University of Southern California School of Medicine, Los Angeles.
1971-present	Research Consultant, Professional Staff Association, Los Angeles County-U.S.C. Medical Center.
1964-1968	Assistant Professor of Pathology, U.S.C. School of Medicine, Los Angeles.
1964-1969	Dernham Sr. Fellow in Oncology, American Cancer Society (Calif. Div.) - Research in tumor immunology.

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1962-1964	Clinical Instructor in Pathology, University of California School of Medicine, San Francisco.
1962-1964	Chief, Clinical Laboratories, Veterans Administration Hospital, San Francisco.
1958-1962	Resident in Pathology, University of California Medical Center program, part-time research during this period.
1957-1958	Intern (straight medicine), University of California Medical Center, San Francisco.

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John W. Parker, M.D.

PUBLICATIONS

1. Parker, J.W., Grodsky, G.M. and Carbone, J.W. A study of the metabolites of florantyrone. Gastroenterology, 41:563, 1961.
2. Parker, J.W., Elevitch, F.R. and Grodsky, G.M. Binding of fluorescent insulin to intracellular antibodies in guinea pigs immunized with insulin. Proc. Soc. Exp. Biol. Med., 113:48, 1963.
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4. Parker, J.W., and Lichtenstein, L. Severe hepatic involvement in chronic disseminated histiocytosis X. Am. J. Clin. Path., 40:624, 1963.
5. Paddock, R.B., Parker, J.W., and Guadagni, N.P. The effects of methoxyflurane on renal function. Anesthesiology, 25:707, 1964.
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8. Parker, J.W., Wakasa, H., and Lukes, R.J. Cytoplasmic fibrils in mixed lymphocyte cultures. Blood, 29:608, 1967.
9. Parker, J.W., Wakasa, H., and Lukes, R.J. Canine and Burkitt's lymphomas. Lancet, 1:214, 1967.
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11. Smith, W.C., Kaneshiro, M.M., Goldstein, B.D., Parker, J.W., and Lukes, R.J. Gaucher cells in chronic granulocytic leukemia. Lancet, 2:780, 1968.
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22. Tindle, B.H., Parker, J.W. and Lukes, R.J. "Reed-Sternberg cells" in infectious mononucleosis? (A report of eight cases.) Am. J. Clin. Path. 58: 607-617, 1972.
23. Parker, J.W., O'Brien, R.L., Lukes, R.J., Steiner, J. and Paolilli, P. Periodate-induced lymphocyte transformation. 1. Inhibition by sulfhydryl reducing agents and sugars. Immunol. Comm. 1(3):263-277, 1972.
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31. Parker, J.W. and Streng, C. Lymphocyte transformation in steroid deficient mice. In preparation.
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Source: https://www.industrydocuments.ucsf.edu/docs/lzyl0000

ABSTRACTS

1. Parker, J.W., Wakasa, H. and Lukes, R.J. Defective lymphocyte transformation in Hodgkin's disease. Sixth Internat. Congress of the Internat. Acad. Path., Kyoto, Japan, Oct. 13-19, 1968.
2. Lukes, R.J. and Parker, J.W. A critical re-evaluation of lymphocyte transformation in Hodgkin's disease. Sixty-Sixth Annual Meeting of the Am. Assn. Path. Bact., 1969, San Francisco. Am. J. Path. 55:22a, 1969.
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4. Smith, W.C., Kaneshiro, M.M., Goldstein, B.D., Parker, J.W. and Lukes, R.J. Gaucher cells in chronic granulocytic leukemia. Annual Meeting of the Internat. Acad. Path., 1969, San Francisco. Lab. Invest 20:603, 1969.
5. Parker, J.W., O'Brien, R.L., Lukes, R.J. and Steiner, J. Inhibition of sodium periodate induced lymphocyte transformation by reducing agents. Fed. Proc. 31:796, 1972.
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R: REDACTED MATERIAL

BIOGRAPHICAL SKETCH — RICHARD L. O'BRIEN, M.D.

Name:	Richard L. O'Brien, M.D.
Academic Title:	Associate Professor of Pathology
Date of Birth:	
Place of Birth:	REDACTED
Citizenship:	
Sex:	Male
Marital Status:	REDACTED

EDUCATION:

Institution and Location	Degree	Year	Scientific field
Creighton University, Omaha, Neb.	REDACTED		Physiology
Creighton University, Omaha, Neb.			Medicine

HONORS:

Post-sophomore Research Fellowship, USPHS, 1957-1958
Alpha Omega Alpha, 1959
White House Fellowship Finalist, 1966
Special Fellow, National Cancer Institute, 1967-1969

RESEARCH AND PROFESSIONAL EXPERIENCE:

1970-present:	Associate Professor of Pathology, University of Southern California School of Medicine, Los Angeles.
August 1966-present:	Research on the mechanisms of chemical and viral oncogenesis and control of chromosome replication.
1966-1970:	Assistant Professor of Pathology, University of Southern California School of Medicine, Los Angeles.
1964-1965:	Capt. M.C., Department of Molecular Biology, Walter Reed Institute of Research, Washington, D.C. Research on the interaction of anti-malarial compounds with DNA, the effect of these interactions on the synthesis of nucleic acids, and the relationship of these interactions to the biologic activity of the antimalarials.
1962-1964:	Postdoctoral fellow in biochemistry, Enzyme Institute, University of Wisconsin, Madison. Research on energy transduction in mitochondria and movement of substances across biological membranes.

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1960-1962	Intern and Assistant Resident (Medicine), 1st Medical Division, Bellevue Hospital, New York, N.Y.
1957-1958	Postsophomore research fellow of USPHS, Creighton University School of Medicine, Omaha, Nebraska. Research on the relationships between the reticuloendothelial system and the action of cortisone and STH; research on the relationships between the sympathetic nervous system and blood pressure control.
June and July 1957:	Research fellow of the Allergy Foundation of America, Veterans Administration Hospital, Omaha, Nebraska. Research of serotonin and histamine in sensitized guinea pig uteri.

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Richard L. O'Brien, M.D.

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3. Wilhelmj, C. M., O'Brien, R. L., and Mc Carthy, H. H.: Sympathetic imbalance and blood pressure homeostasis. Physiologist, 1:86, 1958.

4. O'Brien, R. L., and Koszewski, B. J.: Humoral factors in myeloproliferative disorders. Clin. Res., 7:385, 1959.

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